



DEPARTMENT OF HEALTH & HUMAN SERVICES

March 25, 1999

Food and Drug Administration
Rockville MD 20857

Certified Mail
Return Receipt Requested

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Re: In the matter of Eugen O. Grecu, M.D., Ph.D.

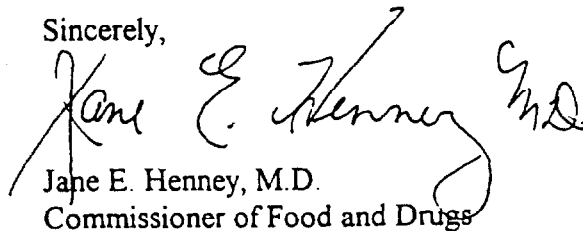
Mr. Gregory F. Gilbert, Esq.
Counsel for Eugen O. Grecu, M.D., Ph.D.
8776 Killdee, Suite 100
Orangevale, CA 95662

Dear Mr. Gilbert:

Please see the enclosed opinion in which I am affirming and adopting the Summary Decision of the Presiding Officer in the above-referenced matter. I have found that Dr. Grecu has repeatedly or deliberately failed to comply with the requirements of 21 CFR Parts 312, 50 or 56, and has repeatedly or deliberately submitted to FDA or to the sponsor false information in required reports.

In accordance with 21 C.F.R. § 312.70(b), you are hereby advised that Dr. Grecu is no longer eligible to receive investigational new drugs. Please direct Dr. Grecu to return all investigational drugs currently in his possession to their supplier. Further, by this letter, I am providing a copy of the Summary Decision to counsel for the Center for Drug Evaluation and Research and to the Dockets Management Branch to be placed on display in the public reading room.

Sincerely,


Jane E. Henney, M.D.
Commissioner of Food and Drugs

cc: Peter Rheinstein, M.D., J.D., HFY-40
Brian J. Mallin, Esq., HFY-20
Barbara Stradling, Esq., GCF-1
Denise Zavagno, Esq., GCF-1
Kara Parker, Esq., GCF-1

00R-0176

SD 1

In the Matter of Eugen O. Grecu, M.D., Ph.D

I have reviewed the record of the regulatory hearing regarding whether to disqualify Dr. Grecu from receiving investigational new drugs. I have considered the Summary Decision of the Presiding Officer and all other portions of the administrative record.

Following are my conclusions on the specific charges:

1. On the first charge, I am affirming the decision of the Presiding Officer that Dr. Grecu violated 21 CFR § 312.62(b) by deliberately or repeatedly failing to maintain adequate case histories for both the glipizide and medroxyprogesterone acetate ("MPA") study.
2. On the second charge, I am affirming the decision of the Presiding Officer that Dr. Grecu violated 21 CFR § 312.70(a) by deliberately or repeatedly submitting false information to a sponsor in required reports.
3. On the third charge, I am affirming the decision of the Presiding Officer that the Center has not shown that Dr. Grecu violated 21 CFR § 312.60 by failing to obtain informed consent of subjects.
4. On the fourth charge, I am affirming the decision of the Presiding Officer that Dr. Grecu violated 21 CFR § 312.62(c) by failing to retain the records of the MPA study for two years after the investigation had been discontinued.

I am hereby affirming and adopting the decision of the Presiding Officer in this matter. I find that Dr. Grecu has repeatedly or deliberately failed to comply with the requirements of 21 CFR parts 312, 50, or 56, and has repeatedly or deliberately submitted to FDA or to the sponsor false information in required reports.

In accordance with 21 CFR 312.70(b), I hereby find that Dr. Grecu is no longer eligible to receive investigational drugs.


Jane E. Henney, M.D.

Commissioner of Food and Drugs

Date

9/11/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. FOOD AND DRUG ADMINISTRATION
REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY
EUGEN O. GRECU, M.D., Ph.D.
FROM RECEIVING INVESTIGATIONAL NEW DRUGS

SUMMARY DECISION OF THE PRESIDING OFFICER

1. INTRODUCTION

Pursuant to Title 21 of the Code of Federal Regulations ("C.F.R.") Parts 16 and 312, the United States Food and Drug Administration ("FDA" or "Agency") has reviewed the motions for summary decision and supporting memoranda and exhibits submitted by FDA's Center for Drug Evaluation and Research ("CDER" or "Center") and Eugen O. Grecu, M.D., Ph.D., in response to the hearing request to consider the proposal of FDA's Center to disqualify Dr. Grecu from being eligible to receive investigational new drugs, pursuant to 21 C.F.R. §312.70.¹ The Center contends that Dr. Grecu should be disqualified for the following reasons: (1) failure to prepare

¹ An investigational new drug is defined as "a new drug, . . . or biological drug that is used in a clinical investigation." See 21 C.F.R. § 312.3(b). A new drug, which includes an approved drug that is proposed for a new use, is defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act. See also 21 C.F.R. § 310.3.

and maintain adequate and accurate case histories, in violation of 21 C.F.R. § 312.62(b); (2) submission of false information to the sponsor, in violation of 21 C.F.R. § 312.70; (3) failure to obtain informed consent from subjects, in violation of 21 C.F.R. § 312.60; and (4) failure to retain records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or, if no application is to be filed or, if the application is not approved for such indication, failure to retain records until two years after the investigation is discontinued and FDA is notified, in violation of 21 C.F.R. § 312.62(c).

This document constitutes my summary decision on the motions submitted in connection with the hearing pursuant to 21 C.F.R. §§ 16.26(b). This decision will be referred to the FDA Commissioner for a final determination on this matter. See 21 C.F.R. § 16.95 and 312.70.

2. BACKGROUND

In October 1989, Dr. Grecu,² as investigator³, began a clinical investigation under an

² Dr. Grecu is currently employed as a physician at the Aoki Diabetes Research Institute, Sacramento, California. Dr. Grecu is a graduate of the School of Medicine of the Medico-Pharmaceutical Institute, Cluj, Romania, where he earned an M.D. (1964) and Ph.D. (endocrinology, 1972). After arriving in the United States, Dr. Grecu did post graduate work in internal medicine at St. Joseph Mercy Hospital (Pontiac, Michigan; 1974-1976, and in endocrinology and metabolism at the University of California (Davis; 1976-1978). From 1978 - 1992, he was employed at the Veterans' Affairs ("VA") Outpatient Clinic, Sacramento, California and ended his career there as Chief of Endocrinology and Metabolism and Chief Medical Officer. He held a part-time appointment as Associate Professor of Internal Medicine at the University of California - Davis. Dr. Grecu is certified by the American Board of Internal Medicine and American Board of Endocrinology and Metabolism. Memorandum from Director, Division of

Investigational New Drug application ("IND")⁴ for the drug glipizide, for the sponsor⁵ [] under IND [] Center Exhibit ("CX") 5 at 1; see also CX 6 at 2-3. The study was conducted in the Sacramento Veteran's Administration ("VA") Outpatient Clinic in Sacramento, California. By May 1990, 42 subjects had been enrolled in the study. Id.

After a site monitoring visit in May 1990, [] the contract research organization employed by [] to monitor the investigation, raised questions regarding potential altering of laboratory records of fasting blood sugar values to meet protocol entry criteria. CX 6 at 3.

[] Medical Director, Dr. [] visited the study site in Sacramento, reviewed the study data, and was reportedly convinced that the laboratory values had been changed. Id. [] subsequently terminated the study, and no new subjects were entered. CX 5 at 1. In May 1990,

Scientific Investigations, CDER, to Associate Commissioner for Regulatory Affairs, FDA, dated September 14, 1994, AR A at 3; CX 2 at 3-4.

³ An investigator is defined as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to the subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team." See 21 C.F.R. § 312.3(b).

⁴ 21 C.F.R. § 312.20 requires a sponsor to "submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to [21 C.F.R.] § 312.2(a)." A clinical investigation is defined as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects." 21 C.F.R. § 312.3(b).

⁵ A sponsor is "a person who takes responsibility for and initiates a clinical investigation." 21 C.F.R. § 312.3(b).

[] notified the VA Institutional Review Board⁶ ("IRB") and FDA of the discrepancies in the laboratory records. CX 6 at 3.

The VA conducted an investigation and subsequently suspended Dr. Grecu's clinical privileges to do research. CX 5 at 1. The VA review revealed discrepancies in another study conducted by Dr. Grecu, investigating the effects of medroxyprogesterone acetate ("MPA") as an antagonist of adverse glucocorticoid effects on calcium metabolism in male patients. *Id.* at 2. Dr. Grecu was sponsor-investigator⁷ of this study, which was conducted at the Sacramento VA Outpatient Clinic under IND[] and which involved at least twenty-four patients with glucocorticoid-induced osteoporosis. He reported the results of this research in Calcified Tissue International (1990) 46:294-299. The VA committee review disclosed numerous discrepancies in the reporting of information from these subjects. *Id.*

FDA conducted a for cause inspection of Dr. Grecu, from June 24, 1991 to July 30, 1991.

CX 5 at 3. At that time, FDA had not previously inspected Dr. Grecu nor the Sacramento VA

⁶ IRB means "any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research." 21 C.F.R. § 50.3(i).

⁷ A sponsor-investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part includes those applicable to an investigator and a sponsor. 21 C.F.R. § 312.3 (b).

Outpatient Clinic. The inspection, conducted by Mr. Merlyn L. Wurscher⁸ and Robert Young, M.D., Ph.D., confirmed the discrepancies reported by [] and the VA review committees. Id. at 1-2.⁹ On July 29, 1991, Mr. Wurscher issued an FDA Form 483 (List of Inspectional Observations) to Dr. Grecu and discussed with him the deficiencies found in the investigation. Id. at 4.

In response to the inspectional findings, on May 15, 1992, Frances O. Kelsey, Ph.D., M.D., Director of the Center's Division of Scientific Investigations, Office of Compliance, sent Dr. Grecu a "Notice of Adverse Findings" letter citing his specific violations of FDA regulations. CX 1. The letter offered him an opportunity to respond to the allegations in writing or at an informal conference, or to enter into a consent agreement that would rescind his eligibility to receive investigational drugs. Id. at 6. The letter concluded by stating that, in the absence of a consent agreement or a satisfactory response, Dr. Grecu would be offered the opportunity for a regulatory hearing on these matters under 21 C.F.R. Part 16. Id. at 7.

On July 27, 1992, Dr. Grecu attended an informal conference with the Center. See CX 2. The Center was represented by Drs. Kelsey, Young, Alan Lisook, Betty Jones, and George Prager.

⁸ At the time of this inspection, Mr. Wurscher worked out of FDA's San Jose Resident Post/San Francisco District Office. CX 5 at 3.

⁹ Dr. Young worked on the investigation from June 24-28, 1991. Mr. Wurscher conducted the remainder of the investigation alone. CX 5 at 3.

Dr. Grecu was accompanied by his attorney, Mr. Gregory Gilbert¹⁰, and a witness,

Dr. [

] Id. at 1. The Center representatives and Dr. Grecu discussed the FDA investigators' findings detailed in Dr. Kelsey's May 15, 1992 letter and Dr. Grecu was given an opportunity to explain and respond to the allegations against him. See CX 2.

3. PROCEDURAL HISTORY

The Center found Dr. Grecu's explanation offered at the informal conference to the allegations against him to be inadequate. By letter dated October 14, 1994, Ronald G. Chesemore, FDA Associate Commissioner for Regulatory Affairs, informed Dr. Grecu that he would be given an opportunity for a regulatory hearing under 21 C.F.R. Part 16, to determine whether he should be disqualified from receiving investigational new drugs. CX 3 at 1. This Notice of Opportunity for Hearing ("NOOH")¹¹, was issued pursuant to 21 C.F.R. §§ 312.70 and 16.22. See CX 3. On November 1, 1994, Dr. Grecu requested a hearing in a letter addressed to Mr. Stan Woolen,

¹⁰ Mr. Gilbert is also the Administrative Director of Aoki Diabetes Research Institute. CX 2 at 10-11.

¹¹ 21 C.F.R. Part 16 provides: "FDA will give to the party requesting the hearing reasonable notice of the matters to be considered at the hearing, including a comprehensive statement of the basis for the decision or action taken or proposed that is the subject of the hearing and a general summary of the information that will be presented by FDA at the hearing in support of the decision or action." 21 C.F.R. § 16.24(f).

Associate Bioresearch Program Coordinator, FDA. See CX 4. The letter also provided a response to the charges listed in the NOOH. Id.

Starting on March 28, 1995, the Agency began attempting to schedule a hearing, but the parties were unable to agree on a suitable date or location for the hearing. See AR E. As Presiding Officer, I provided both the Center and Dr. Grecu with information on Part 16 hearing procedures, as well as copies of 21 C.F.R. Parts 16 and 10 and § 312.70, in a letter dated August 10, 1995. See AR Mc. The letter also provided an opportunity for each party to select potential hearing dates from a list of available dates for the hearing to be held at FDA. Id.

In response to this letter, the parties selected conflicting times for a proposed hearing and indicated their intent to file motions for summary decision in the near future. See AR Tabs N, P, and Q.¹² Therefore, scheduling the hearing was held in abeyance, pending receipt and consideration of the motions for summary decision.

The Center submitted its Motion for Summary Decision and Memorandum in Support of CDER's Motion for Summary Decision ("Center Motion") on October 24, 1995. Dr. Grecu submitted a Memorandum in Opposition of CDER's Motion for Summary Decision and Memorandum in Support of the Motion for Summary Decision by Investigator E. Grecu, M.D. ("Grecu Motion"),

¹² In addition, Dr. Grecu requested that the hearing be held in Sacramento, California, for the convenience of a number of his proposed witnesses. AR P.

dated February 29, 1996, and received by the Presiding Officer on March 5, 1996. The Center filed a Reply Memorandum in Support of CDER's Motion for Summary Decision and in Opposition to Dr. Grecu's Motion for Summary Decision ("Center Reply"), dated April 4, 1996, and received by the Presiding Officer on April 5, 1996.

4. REGULATORY FRAMEWORK

FDA's regulations governing the clinical evaluation of investigational new drugs are set forth in 21 C.F.R. Part 312. Regulations regarding informed consent and IRBs applicable to clinical investigations are set forth in 21 C.F.R. Parts 50 and 56.

Section 312.70 of the regulations provides for the disqualification of clinical investigators. That section provides, in pertinent part, as follows:

After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50, or Part 56, or has deliberately or repeatedly submitted false information to the sponsor in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

21 C.F.R. § 312.70(b).

According to 21 C.F.R. § 16.26, the Presiding Officer of a Part 16 hearing is authorized to issue a summary decision on any issue in the hearing¹³ if the Presiding Officer determines from material submitted in connection with the hearing, or from matters officially noticed, that there is no genuine and substantial issue of fact respecting that issue. 21 C.F.R. § 16.26(b). A summary decision may be issued any time after the receipt by FDA of a request for a hearing submitted in response to a NOOH. Id.

The standard for summary decision contained in 21 C.F.R. § 16.26(b) mirrors that found in Rule 56 of the Federal Rules of Civil Procedure (Fed. R. Civ. P.), which provides that summary judgment "shall be rendered . . . if there is no genuine issue as to any material fact and [] the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c). Therefore, the Presiding Officer may be guided by the body of law developed under Rule 56 in determining whether summary decision is warranted in this case. See 53 Fed. Reg. 4613, 4614 (February 17, 1988).

On a Rule 56 motion, a court must determine whether there are issues of fact in dispute to be decided in a trial on the merits. Celotex Corp. v. Catrett, 477 U.S. 317 (1986). The party moving for summary judgment bears the burden of establishing the absence of a genuine issue of material fact. Adickes v. S. H. Kress, 398 US 144,157 (1970). A party opposing a motion for

¹³ For purposes of this section, a hearing commences upon receipt by FDA of a request for hearing submitted under § 16.22 (b).

summary decision has the burden of showing that a rational trier of fact could find for the nonmoving party and that there is a "genuine issue for trial." 475 U.S. 574, 586 (1986); see also First National Bank of Arizona v. Cities Service Co., 391 U.S. 253, 288-9 (1968) (where the record taken as a whole could not lead a rational trier of fact to find for the nonmoving party, there is no "genuine issue for trial"). To fulfill this burden, the nonmoving party "must set forth specific facts showing that there is a genuine issue for trial." Fed. R. Civ. P. 56(e); Matsushita Electrical, 475 U.S. at 586; First National Bank, 391 U.S. at 289. The mere existence of a scintilla of evidence in support of the nonmoving party's position will be insufficient. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 252 (1986).

As set forth in the NOOH and again in the Center's Motion, the Center alleges that Dr. Grecu repeatedly or deliberately violated Federal regulations in his capacity as a clinical investigator of the investigational drugs glipizide and MPA in at least four respects: (1) he failed to prepare and maintain adequate and accurate case histories (21 C.F.R. § 312.62(b)); (2) he submitted false information in required reports to the sponsor (21 C.F.R. § 312.70); (3) he failed to obtain informed consent of subjects (21 C.F.R. § 312.60); and (4) he failed to retain records for a period of two years following the date a marketing application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified (21 C.F.R. § 312.62(c)). Accordingly, if the evidence as currently submitted demonstrates that no genuine and substantial issue of fact exists as to any one of these alleged violations and shows that any of the violations occurred repeatedly or deliberately, the Presiding

Officer may recommend to the Commissioner that Dr. Grecu be disqualified.

21 C.F.R. § 312.70(b).

5. ANALYSIS

Charge I. Dr. Grecu violated 21 C.F.R. § 312.62(b)¹⁴ by failing to prepare and maintain adequate and accurate case histories.

In the NOOH, the Center charges Dr. Grecu with failing to maintain adequate and accurate case histories in a study of the investigational drug glipizide, conducted for sponsor [] under IND [] and in a study of the drug medroxyprogesterone acetate ("MPA") (IND [] in which Dr Grecu acted as both sponsor and investigator. I will address the charges raised in connection with these two studies separately.

A. Glipizide Study

The purpose of the glipizide study was to investigate the safety and efficacy of using glipizide to lower the daily insulin requirements of Type 2 diabetics. CX 8 at 5. In order to enter the

¹⁴ 21 C.F.R. §312.62(b) provides that "[a]n investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational drug or employed as a control in the investigation."

medication phase of the study, subjects first had to complete the baseline phase. The purpose of the baseline phase was to ensure that study subjects had a stable baseline glucose level, documented by fasting plasma glucose values. CX 5 at 6. During this phase, subjects visited the clinic one morning a week for a fasting blood glucose ("BG") test. Id. at 17. The protocol provided that the weekly BG test was to be taken by "phlebotomy venous sample," or by drawing blood directly from a vein. Id. at 15. In order to proceed into the medication phase of the study, subjects had to have BG values of between 160 mg/dL and 300 mg/dL¹⁵, within 60 mg/dL of each other, on three consecutive visits. Id. at 17. Subjects unable to meet these criteria after five baseline visits were excluded from the study. Id. at 18.

According to the Center, changes were made in thirty-three separate instances to the three-part Standard Form 546 slips on which BG results were recorded. These altered values were subsequently entered onto the subjects' case report forms. CX 5 at 11-15. Center investigators noted these discrepancies by comparing the test results on the daily laboratory instrument log sheet and the VA Outpatient Clinic's cumulative computer files with the results on the three parts of the Standard Form 546 and the case report forms. CX 5 at 10. The alterations were made by writing over or whiting out the initially recorded values. CX 3 at 2. No notations were made on the report slips to indicate when a change was made, or to identify the person responsible for making a change. Id. Twenty-seven of the alterations resulted in entering test subjects into the

¹⁵ On February 2, 1990, the upper end of this range was increased to 350 mg/dL by study Amendment C. See CX 8.

medication phase of the study who, based on the original values transcribed on the slips, otherwise would have been ineligible for entry into the study. CX 6 at 9.

The Center points out that Dr. Grecu has never disputed the documented alterations to the slips. In his November 1, 1994 response to the NOOH, Dr. Grecu attributes sixteen of the changes to "laboratory-originated transcription" errors, one to his own transcription error, and alleges that the remaining sixteen discrepancies represent the results of repeat "fingerstick" BG tests¹⁶ that he ordered an hour after the initial results were obtained. CX 4 at 1-2. He argues that the transcription errors should not be considered a violation of FDA regulations because he could not have prevented them and would have corrected both the "laboratory-originated transcription" errors and his own transcription error when preparing the data report to the sponsor at the end of the study. Id. at 2; see also CX 2 at 51-2. He argues that the repeat fingerstick BG tests do not constitute "false data" but rather are "equally valid" to the venous BG test, although he acknowledges that he erred in failing to note the change in BG value, which "certainly was not deliberate." CX 4 at 2 (emphasis in original).

Dr. Grecu's explanation fails to raise any genuine issue of fact for consideration. Although he never had the opportunity to prepare a final report because his study was terminated prematurely, he still was required by regulation and the study protocol to prepare and maintain accurate

¹⁶ "Fingerstick" BG tests analyze blood taken from the capillaries of the fingers, in contrast with venous tests in which the blood is drawn directly from a vein. CX 2 at 20.

records. 21 C.F.R. § 312.62(b); CX 8 at 30¹⁷. Dr. Grecu, as clinical investigator, had the primary responsibility for ensuring the accuracy of relevant BG values throughout the study, and particularly prior to entering subjects into the medication phase of the study.

The Center accurately notes, and Dr. Grecu admits, that the sixteen discrepancies that Dr. Grecu attributes to a repeat of the BG test were not authorized by the protocol. See CX 8; see also CX 2 at 27. The protocol makes no provisions for repeat BG tests until the medication phase of the study. CX 8 at 19. Nor does it permit the use of fingerstick BG tests, instead requiring venous samples of blood to be drawn and analyzed in the laboratory. Id. at 15.

Dr. Grecu justifies these departures, however, based on his "clinical judgment" and on the basis that the protocol did not explicitly prohibit them. He explains that

[t]he idea of the study, as designed, was to enroll "stable" type 2 diabetic patients. I have been treating these patients for years, knew them well, and I was in the best position to judge their diabetes "stability," much more so than just relying on the BG range chosen in the study protocol . . . When, on a few occasions, a fasting BG did not fit the test criteria alleged to establish "stability" by the study protocol, in a particular diabetic patient well known to me and with a quite stable diabetes control, I exercised my clinical judgement (sic) and ordered a repeat BG within 1 hour on the same morning, with the patient still fasting. No diabetic on intermediate acting insulin therapy taken the night before (duration 24 hours) will have the same BG when tested an hour later the same morning. I, and every other physician, would therefore anticipate a different

¹⁷ Specifically, the protocol provided: "The investigator or sub-investigator is responsible for assuring that study data is completely and accurately recorded on the case report forms supplied by the sponsor." CX 8 at 30.

number, which might fit the test criteria required by the protocol. The patients I had enrolled already fulfilled all the criteria required by the protocol and were stable diabetics in my clinical judgment; if the repeat BG would fit the somewhat arbitrary range criteria of the protocol, the patient could continue in the study. If not, I would drop him from the study . . . Uniformly I have been assured that using the fingerstick BG was a valid practice given the skilled person administering the test . . .

Grecu Motion at 20.¹⁸

Dr. Grecu contends that the protocol permitted repeat BG tests in the medication phase of the study. As the Center accurately notes, however, this provision permitting repeat BG tests (on the next day, notably-- not one hour later) in the medication phase is entirely irrelevant to the question of whether such tests were permitted in the baseline entry phase of the study.

Dr. Grecu's argument simply misses the point. In agreeing to participate in the study, Dr. Grecu agreed to abide by all requirements and restrictions of the protocol, including the following relevant provisions:

¹⁸ During the informal conference with the Center in 1992, Dr. Grecu attempted to justify his departure from the protocol by presenting testimony from his witness Dr. [] who explained that, in his opinion, the protocol design was inadequate in using only a few fasting blood sugar results as criteria for gaining access to the study instead of a hemoglobin A1C test, which measures glucose control over longer periods of time. CX 2 at 35-36, 53-58.

1. Modifications in Protocol. Neither the investigator nor [] will modify this protocol without first obtaining the concurrence of the other. The party initiating a modification will confirm it in writing and appropriate IRB approval shall be obtained, if necessary, PRIOR to implementation of the change.

2. Departures from Protocol for an Individual Patient. A departure from protocol shall only be allowed for an individual patient if there is an emergency or accident where the patient's safety is at risk. In the event of this occurrence, the investigator shall inform

[] Such contact shall be made as soon as possible to permit a decision as to whether or not the patient involved should continue in the study.

CX 8 at 26 (emphasis in original).

Dr. Grecu acknowledges that he never attempted to modify the protocol pursuant to the above provisions, stating that, despite his belief that the protocol was insufficient to take into account fluctuating blood glucose values, he "did not have the chance to raise it with the sponsor."

CX 2 at 18. He noted later that because the protocol previously had been formally modified in ways suggesting greater discretion for the investigator, he felt "absolutely comfortable" repeating the BG test without seeking a formal modification to the protocol. Id. at 40.

Dr. Grecu's explanation for altering the laboratory tests to delete valid BG results and instead reflect the results of "repeat" fingerstick tests is unacceptable. Accuracy of the BG tests was critical to determining both the effectiveness of the investigational drug and subject selection criteria. While patient risk was low, a subject inappropriately assigned to the treatment group by altered baseline data was placed at increased risk for hypoglycemia. CX 6 at 5. As the Center

noted, twenty-seven of the thirty-three subjects whose laboratory slips reflected such alterations would have been ineligible for the study absent the "transcription errors" and other alterations, and thus may have been placed at risk. Id. at 9.

The evidence submitted on this charge clearly establishes that Dr. Grecu deliberately and repeatedly altered the values on laboratory slips.¹⁹ In fact, Dr. Grecu himself admits that his actions in altering the BG values on sixteen of thirty-three forms were both deliberate and in contradiction to the protocol, which permitted neither fingerstick tests nor repeat tests for the baseline/entry phase of the study.²⁰ CX 2 at 27. The values entered onto the forms were thus inaccurate in that they did not reflect the subject's BG values obtained in accordance with the clear specifications of the protocol.

For the reasons stated above, Dr. Grecu has failed to raise any genuine and substantial issue of

¹⁹ Moreover, there is some evidence to suggest that Dr. Grecu attempted to alter the BG values in the VA computer to match those on the altered laboratory slips. See CX 9. According to Laboratory Supervisor [] Dr. Grecu requested that [] alter the computer's BG values of 8-15 patients. CX 9 at 3. Dr. Grecu's request of [] took place on May 25, 1990, three days after [] review of the records that called Dr. Grecu's practices into question, and only four days prior to the visit of [] Medical Director, Dr. [] Id.

²⁰ Dr. Grecu stated that he only performed a fingerstick BG test when the patient could not return the following day for a venous BG test, although no documentation was presented to establish this. CX 2 at 28-29, 122. Dr. Grecu stated that his patients were "very eager" to participate in the study, so he was reluctant to drop a patient when he did not make the entry criteria as stated in the protocol. Id. At 122-3. Instead, Dr. Grecu stated that he could offer his patients an opportunity for a re-test within half an hour or on the following day. Id.

fact that precludes summary decision as a matter of law on whether Dr. Grecu failed to prepare and maintain adequate and accurate case histories. Thus, for the glipizide study, the Center has demonstrated that Dr. Grecu repeatedly and deliberately violated 21 C.F.R. § 312.62(b).

B. MPA Study

The Center also charges that Dr. Grecu failed to prepare and maintain adequate and accurate case histories for the study he conducted of medroxyprogesterone acetate, or MPA, in violation of 21 C.F.R. § 312.62(b).

In the MPA study (IND[] conducted at the VA Medical Center in Sacramento, California, Dr. Grecu sought to prove his hypothesis that MPA is an effective therapy for glucocorticoid-induced osteoporosis. CX 5 at 18. Toward that end, he treated a group of patients suffering from glucocorticoid-induced osteoporosis with MPA and recorded their trabecular bone density ("TBD")²¹ values over the span of a year to assess the effect of the MPA. *Id.* at 18-19; Grecu Exhibit ("GX") C at 1. Study subjects were to undergo computerized tomography ("CT") scans immediately prior to treatment with MPA (the baseline or 0-month time period) as well as at a 6-month and 12-month interval to assess whether their TBD values were increasing in accordance with Dr. Grecu's theory. CX 5 at 18-19.

²¹ TBD determinations were conducted at the VA Medical Center in Martinez, California ("VA Martinez.")

The Center reported that FDA investigators attempted to obtain the case histories for the subjects of the MPA study, both during FDA investigations in June and July 1991, and during Dr. Grecu's informal conference with Center staff in Rockville, Maryland, on July 27, 1992. CX 3 at 5.

Dr. Grecu stated on all of these occasions that he no longer had these case histories in his possession. He stated in his response to the NOOH dated November 1, 1994:

As I explained during the informal conference with CDER on July 27, 1992, in order to facilitate the collection and safe-keeping of the data generated during that length study (5 years), I chose to concentrate it all in a master data book. This master data book was lost in 1989, shortly after data was statistically analyzed and prepared for publication. When in 1991 this study was reviewed by the FDA investigators, I was able to provide them only with the analyzed and tabled data I used for publication two years earlier, but not with the raw data contained in the lost master data book.

Id. at 2-3; see also CX 2 at 67. The results of the MPA study were set forth in a paper entitled "Effective Therapy of Glucocorticoid Induced Osteoporosis with Medroxyprogesterone Acetate" published in Calcified Tissue International (1990) 46:294-299. Dr. Grecu submitted this article to FDA in partial fulfillment of his responsibility, as sponsor of IND[] to submit an annual progress report (21 C.F.R. § 312.33).²² The Center compared the published data with the pertinent VA hospital records in an attempt to reconstruct the case histories for these study subjects.

²² Dr. Grecu stated that he submitted this article for publication in April 1989. CX 2 at 66.

In the NOOH, the Center outlined a number of discrepancies that became apparent upon comparison of these two sets of records, including:

1. Individual subjects' computerized tomography trabecular bone density ("TBD") determinations were reported as if they were determinations from several subjects;
2. Subjects were included in the control group while they were receiving MPA;
3. Computerized tomography TBD determinations were reported as being taken at defined times, e.g., day 0, but VA records did not confirm that the TBD determinations had been taken on or near the defined time reported; and
4. Intervals between computerized tomography TBD determinations were incorrectly reported.

CX 3 at 5-10.

Dr. Grecu admits that the only case histories he kept were in the master data book.²³ CX 4 at 2.

The only data that Dr. Grecu can present as evidence of the case histories lost with the master data book is the published article, which, as Dr. Grecu himself points out, is rife with errors.

Dr. Grecu freely admits that eleven of the twenty-three study subjects included in his article were misidentified. CX 4 at 3. He blames the misidentification on a number of factors, including the inadequacies of the VA Martinez computer system; the fact that some TBD determinations were performed at facilities other than the VA Martinez; and Dr. Grecu's "adjustment" of some TBD

²³ Although the data book disappeared before Dr. Grecu could verify the data he planned to use in the article, he apparently did not hesitate to present the unverified data for publication.

values.²⁴ CX 2 at 68-70; CX 4 at 3. Dr. Grecu's inability to positively identify nearly one-half of his study subjects is striking evidence of his failure to prepare and maintain adequate and accurate case histories.

Dr. Grecu also admits that two of the correctly identified subjects served as a control for one year and then were treated the subsequent year (19-[] and 9-[] also 14-[] and 5-[] CX 4 at 3; CX 2 at 84-85. There is no indication that the study protocol permitted study subjects to be counted in the study more than once, particularly without making a notation of that fact for data collection and analysis purposes. Hence, the Center accurately contends that Dr. Grecu reported these individual subjects' computerized TBD determinations as if they were determinations from several subjects, and in so doing, failed to keep adequate and accurate case histories for these two subjects.

Dr. Grecu also admits that one subject, 15-[] was erroneously included in the control group even though he was treated with over 20 mg prednisone daily.²⁵ CX 4 at 3. Although Dr. Grecu claims that this was an unintentional error caused by the loss of the master data book and the

²⁴ Dr. Grecu acknowledges that he "adjusted" TBD values in certain situations. CX 2 at 70; CX 4 at 3. If, for example, a TBD measurement failed to include measurements of all 4 lumbar vertebrae, as it was supposed to, he would eliminate the inconsistently measured vertebrae. Id. Or, if a TBD measurement was so "discordant" with other measurements that it, in his opinion, suggested technical error, he would eliminate that value. Id.

²⁵ Dr. Grecu intended to include in the publication only those patients on less than 20 mg prednisone a day. CX 4 at 3; CX 2 at 81.

subsequent difficulty in checking the data prior to publication without the data book, he included this information in his article. Hence, the Center is correct in its charge that this subject's case history incorrectly reflected that he was a member of the control group when in fact he should not have been included in that group.

The Center further alleges that Dr. Grecu reported test results as having been taken at 0, 6, and 12 month intervals even though the dates of the actual tests reveal that the tests were not performed at those intervals, or on the dates listed. CX 3 at 7-10. Dr. Grecu maintains that, although he tried to take the TBD's on dates as close as possible to the required intervals, it was often impossible, due to scheduling difficulties, the patients' serious health problems, and CT scanner failures. CX 4 at 4. Thus, he argues, he based his conclusions solely on the baseline (0) and 12 month values. Id.

Regardless of whether Dr. Grecu based his conclusions on data from all three intervals or only two, he kept inaccurate case histories for the subjects whose test dates and intervals were falsely reported in the published article. In submitting the study for publication, Dr. Grecu represented that the dates and intervals listed for each study subject were accurate, when in fact he was aware that the reported dates and intervals may have been off by several months.²⁶

²⁶ For example, Dr. Grecu reported the baseline (0) TBD examination (date of first administration of MPA) for one subject (9-[]) as taking place on December 23, 1987, when hospital records indicate that the examination took place on September 17, 1987. CX 3 at 8. The 6-month examination, reported as taking place on June 23, 1988, in fact took place on August 26, 1988 (almost 12 months after the baseline examination) according to hospital records.

Furthermore, the evidence cited above indicates that Dr. Grecu's actions with regard to the MPA study discrepancies were deliberate, especially with regard to the case histories for which he intentionally altered and manipulated the dates and intervals. The Ad Hoc Committee Review of the VA Medical Center at Martinez also concluded that numerous instances of data manipulation²⁷ existed in Dr. Grecu's study, all of which supported Dr. Grecu's hypothesis that MPA had a therapeutic effect on glucocorticoid-induced osteoporosis, and that this type of osteoporosis would be progressive if left untreated. CX 7 at 9.

The overwhelming amount of evidence demonstrates the absence of any genuine and substantial issue of fact regarding the charge that Dr. Grecu deliberately and repeatedly altered the case histories of subjects he included in the study he submitted for publication, and thus deliberately and repeatedly failed to prepare and maintain adequate and accurate case histories for these subjects, in violation of 21 C.F.R. § 312.62(b).

Id. The 12-month examination, reported as taking place on December 23, 1988, actually took place on February 7, 1989. Id.

²⁷ The evidence cited by the VA included the alteration of the chronology of the reported TBD values in seven cases in a direction consistent with Dr. Grecu's hypothesis; the fabrication of TBD data in 8 cases; the misassignment of cases to the wrong group (treatment and control); the suppression of information (evidence of decreased bone density) inconsistent with Dr. Grecu's hypothesis; and the suppression of information inconsistent with the assertion that cases were randomly assigned to the two groups (certain individuals were first used as controls and then treated, without notation or identification.) CX 7 at 9. The committee reaffirmed these findings after considering Dr. Grecu's response to the initial review. Id. at 21.

Charge II.: Dr. Grecu violated 21 C.F.R. § 312.70(a)²⁸ by submitting false information to the sponsor in required reports.²⁹

In its motion for summary decision, the Center has restricted consideration of this issue to the glipizide study. Center Motion at 14-15. The Center alleges that false information was submitted in required reports to the sponsor of the glipizide study, because the case report forms contained at least thirty-three separate instances of altered and inaccurate BG values and these forms were periodically reviewed by [] the sponsor, and by [] the firm employed by [] to monitor the investigation. See CX 2 at 59-60.

²⁸ Section 312.70(a) provides the following:

If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50, or part 56, or has submitted to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered but not accepted by the Center for Drug Evaluation and Research or the Center for ~~Biologics Evaluation and Research~~, the investigator will be given an opportunity for a regulatory hearing under part 16 on the question of whether the investigator is entitled to receive investigational new drugs.

²⁹ If the Commissioner determines that the investigator has "deliberately or repeatedly submitted false information to the sponsor in any required report," the Commissioner will disqualify the investigator from being entitled to receive investigational drugs. 21 C.F.R. § 312.70 (b).

The Center references the protocol's provision for inspection of the case report forms, which states:

The investigator or sub-investigator is responsible for assuring that study data is completely and accurately recorded on the case report forms supplied by the sponsor. The last page of the case report form must be signed by the principal or sub-investigator as verification that the data has been reviewed and is complete and accurate. The investigator must have independent records of each patient's data at all times.

Investigators are expected to have each patient's case report form completed promptly and satisfactorily for retrieval by an authorized representative of [] monitoring team.

CX 8 at 30.

The protocol also provides the following instructions:

E. Monitoring

At periodic, pre-scheduled visits, each investigator will permit an authorized representative of [] monitoring team, the FDA, and/or sponsoring client to inspect all case report forms and study related adjunctive data. Case report forms will be compared to supporting data, such as office and/or hospital records containing laboratory, consultation reports, complete history and physical examinations, progress notes, etc.

The investigator will obtain, in the informed consent, permission from the patient for an authorized representative of [] FDA and/or sponsoring client to have access to such source documents for this purpose. These reviews are required by Federal Regulations to insure both adherence to the protocol and the completeness and exactness of the data being entered

CX 8 at 31 (emphasis added).

Dr. Grecu disputes that he submitted false information to the sponsor on a number of grounds. First, he argues, he did not "submit" information to the sponsor, noting that the study was concluded before any final reports were compiled or sent to the sponsor. CX 4 at 1-2; Grecu Motion at 5. Second, he contends that no reports were submitted to "the sponsor," [] apparently contending that it was merely a [] representative" who reviewed the data, and not the sponsor itself. Grecu Motion at 5-6. Finally, he asserts that the relevant regulation only addresses the submission of false information in "formal 'required reports,'" contending that the documents reviewed by the [] and [] representatives were instead "reports of a less formal nature." Id. at 6.

Dr. Grecu's interpretation of the term "submit" is, as the Center points out, unreasonably narrow. Dr. Grecu apparently contends that because he sent nothing directly to the sponsor, he submitted nothing. This interpretation of the term is contrary to common sense, as well as the dictionary definition of "submit." According to Webster's Dictionary (Webster's II New Riverside University Dictionary 1154 (Houghton Mifflin 1988)), "submit" is defined as "[t]o commit (something) to the consideration or judgment of another." Center Reply at 5. Dr. Grecu clearly committed his data forms and case reports "to the consideration or judgment" of the [] representative and the [] representative, as he was required to do under the protocol. CX 8 at 30-31. Hence, he "submitted" the information within the meaning of the term.

His contention that he submitted nothing to "the sponsor" but only to an agent of the sponsor is similarly far-fetched. Once again, the protocol required that the investigator have reports available for inspection by representatives of [] as well as [] the firm with which [] contracted to monitor the progress of the study. CX 8 at 30-31. Documents reviewed by representatives of either firm were thus reviewed by "the sponsor," contrary to Dr. Grecu's assertion otherwise.

Dr. Grecu's assertion that the pertinent regulation addresses only "final" or "formal" required reports is at odds with the protocol itself. The protocol specifically requires that the investigator prepare accurate case report forms for inspection and retrieval by [] representatives or [] representatives. CX 8 at 30-31. As stated in the protocol, "[t]hese reviews are required by Federal Regulations, to insure both adherence to the protocol, and the completeness and exactness of the data being entered." Id. at 31. To hold that these reports were not required would thus contradict the stated intent and purpose of this protocol provision, as well as the purpose of the regulation itself.³⁰

³⁰ The preamble to 21 C.F.R. § 312.70 also sheds light on the intended purpose of the requirement:

A clinical investigator who falsified or destroyed original records of a drug study, and who then submitted false records to a sponsor, would clearly cause the sponsor to maintain false record and to make false reports to FDA. Moreover, were an investigator not required to maintain his or her own records (as distinct from those maintained by the sponsor), FDA would in those cases frequently be precluded from even discovering the falseness of the reports and would then review and perhaps approve drug products on the basis

Finally, it is clear that the information contained in the reports reviewed by [] and [] was in fact "false." The case report forms reviewed by [] and [] representatives were held out by Dr. Grecu as accurate representations of the preclinical test results of the study subjects, when in fact they contained false information. Whether the alterations were the result of "transcription errors" or of unauthorized repeat fingerstick testing, the original, accurate results of the required venous testing were absent from the case report forms when the sponsor's representatives reviewed them. Hence, Dr. Grecu submitted false information to the sponsor in the required case reports.

Furthermore, Dr. Grecu submitted the false information repeatedly, in several patients' case reports. With regard to at least those case reports that were altered as a result of the repeat testing, the submissions were deliberate.

For the reasons stated above, it is apparent that Dr. Grecu has failed to raise any genuine and substantial issue of fact that precludes summary decision as a matter of law on this issue. The Center has demonstrated that Dr. Grecu submitted false information to the sponsor in required reports in violation of 21 C.F.R. § 312.70.

of false data.

52 Fed. Reg. 8798, 8827 (March 19, 1987). As the Center points out, to restrict the interpretation of "required reports" to only the final reports submitted by investigators would lead to a truly undesirable result, in that it would permit an investigator to escape sanction for falsification of data unless his conduct was discovered after he compiled the final report of the investigation. Center Reply at 5.

Charge III: Dr. Grecu violated 21 C.F.R. § 312.60³¹ by failing to obtain informed consent of subjects.

In the NOOH, the Center charges that Dr. Grecu had been unable to demonstrate that he obtained the informed consent of two test subjects in the MPA study. NOOH at 10. The Center's Motion states that informed consent forms for subjects #18 and #22 were not found in the subjects' medical records maintained at the VA hospital, and that Dr. Grecu had admitted that he could not locate the written informed consent for these subjects. Center Motion at 15.

³¹ Section 312.60 provides in relevant part that "...[a]n investigator shall, in accordance with the provisions of part 50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in § 50.23."

Section 50.23 provides circumstances when obtaining informed consent is not feasible, because the subject is confronted with a life-threatening situation necessitating use of the test article immediately, there is no suitable alternative therapy, informed consent cannot be obtained because of an inability to communicate with the subject, and due to insufficient time, or in certain military operations, as determined by the Commissioner.

Regarding documentation of informed consent, section 50.27(a) provides that "[e]xcept as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form."

Section 56.109(c) provides that "[a]n IRB shall require documentation of informed consent in accordance with § 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may, for some or all subjects, find that the requirements in § 50.24 of this chapter for an exception from informed consent for emergency research are met."

Dr. Grecu admits that the informed consent forms could not be located for subject #18, which he attributes to the loss of the master data book and poor VA hospital record keeping. CX 2 at 110; CX 4 at 4; Grecu Motion at 13-14, 25-26. He alleges that the consent form for subject #22, however, is not missing, instead arguing that subject #22 was misidentified. Thus, according to Dr. Grecu, the consent form sought by investigators was for a patient not enrolled in the study, and informed consent was nonexistent³². Id. Dr. Grecu further asserts that the fact that one consent form was not in the file does not evidence a failure to obtain informed consent, because, according to him, a failure to obtain informed consent may only be shown when the subject states that he did not sign an informed consent form. Grecu Motion at 13-14. Finally, Dr. Grecu asserts that failure to demonstrate the existence of one informed consent form does not meet the definition of a "repeated" violation of part 312 for purposes of 21 C.F.R. § 312.70 (b). Id. at 13-14, 25-26.

Regardless of whether Dr. Grecu was able to limit this charge to only one study subject³³ without an informed consent form in his medical records, the Center has not presented proof, other than the missing consent forms, to demonstrate that informed consent was not obtained for these two

³² Dr. Grecu offers no suggestions as to the actual identity of subject #22.

³³ Although Dr. Grecu maintains that the absence of a single consent form cannot constitute a violation performed "repeatedly" for purposes of § 312.70(b), he misstates the law. It is not necessary for CDER to allege multiple violations of the informed consent requirement in order to prevail on this charge; a single violation is sufficient. See § 312.60. The Center is required, however, to demonstrate repeated or deliberate violations of the relevant requirements in order to prevail on a motion for disqualification.

out of the twenty-three study subjects. Neither party has asserted that any of the exceptions under section 50.23 or 56.109(c) apply to remove the requirement for obtaining written informed consent from all study subjects. A disputed issue of fact remains as to whether, regardless of the consent forms' absence, Dr. Grecu ever obtained the written informed consent. For example, it is possible that during the course of the hearing, Dr. Grecu could present evidence sufficient to establish that loss of the master data book and poor VA record keeping caused the informed consent forms to be lost rather than that Dr. Grecu failed to obtain written informed consent in the first instance. It is also possible that the Center could present further evidence sufficient to establish that informed consent was never obtained for these two subjects. In the absence of further evidence or testimony at this time, however, I cannot resolve this charge on summary decision.

Charge IV: Dr. Grecu violated 21 C.F.R. 312.62(c)³⁴ by failing to retain records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

³⁴ The records required to be retained by this provision include those pertaining to the disposition of the drug (21 C.F.R. § 312.62(a)) and adequate and accurate case histories of study subjects, as defined in 21 C.F.R. § 312.62(b).

The Center charges that Dr. Grecu failed to retain records of the MPA study (IND[] for a period of two years following the discontinuation of the investigation and notification to FDA, as required by the regulation. After reviewing the evidence presented by the parties, I find that Dr. Grecu failed to raise any genuine and substantial issue of fact as to the allegation that Dr. Grecu failed to retain the records of the MPA study for two years after completion of the study and notification to the agency.

The Center states that Dr. Grecu admitted to losing his "master data book"³⁵ for the MPA study and admitted that the informed consent forms could not be located for at least two study subjects. Center Motion at 16; see also CX 4 at 2,4. The Center raises a question of Dr. Grecu's conflicting statements regarding how long the records were retained after the study was completed, and emphasized that, even assuming Dr. Grecu did keep the records for two years, he did not notify FDA that he intended to destroy his records two years after the investigation was discontinued, as required by § 312.62(c). Center Reply at 8-9. Finally, the Center emphasized that it was the investigator's responsibility, not that of the VA, to retain records related to the study. Id. at 8.

Dr. Grecu maintains in his motion for summary decision that the master data book contained accurate case history forms for all subjects and that he should not be held accountable for not

³⁵ This master data book, according to Dr. Grecu, contained all relevant data obtained during the study. CX 4 at 2.

having the records on hand because they were "lost." Grecu Motion at 12, 14; see also CX 2 at 75, 77-79. He further alleges that the data book "had to be taken by someone . . . who . . . was interested in hurting [him]." Grecu Motion at 26. He goes on to argue, that the records were in the VA's possession, and he cannot be held accountable for failing to retain them. Grecu Motion at 30. Finally, Dr. Grecu argues that he did not violate this regulation because the two years to retain records ran from the date of completion of the study, and the medical records were kept until that time by the VA but that Dr. Grecu was denied access to the VA records. Id.

In this case, because no marketing application was filed for the indication tested in the study, Dr. Grecu, as the investigator, was obligated to retain the drug disposition information and case histories containing pertinent data for a period of two years following discontinuation of the study and notification to FDA that the study was discontinued. 21 C.F.R. § 312.62(c). When FDA investigators requested these records during the 1991 investigation, Dr. Grecu apparently had no drug disposition or case history information to present to the FDA investigators, except the statistically-modified data published in a journal article³⁶. Although Dr. Grecu maintains that the VA is at fault because it purportedly lost the records of the study patients, it was Dr. Grecu's obligation as an investigator to retain his own copy of the records. The whereabouts of the VA's copy of the records is thus irrelevant to this inquiry, and the only issue is Dr. Grecu's retention of records.

³⁶ "Effective Therapy of Glucocorticoid Induced Osteoporosis with Medroxyprogesterone Acetate." Calcified Tissue International (1990) 46:294-299.

In order to determine whether Dr. Grecu maintained the records for the proper period of time, three dates must be considered and compared: the date the study concluded, the date that Dr. Grecu notified the agency that the study had concluded, and the date the master data book was lost.

According to Dr. Grecu, the MPA study began in 1984 and concluded in "early" 1989.

CX 2 at 68; CX 4 at 2; Grecu Motion at 30. At a minimum, then, if Dr. Grecu had immediately notified the FDA, the records should have been maintained until 1991 (two years following conclusion of the study and immediate notification of FDA). Dr. Grecu offers conflicting dates regarding when the master data book disappeared, but all of the dates asserted by Dr. Grecu would be less than two years following conclusion of the study.³⁷ CX 2 at 67, 87; CX 4 at 2, 3; CX 5 at 32.

There is no evidence to substantiate if and when Dr. Grecu notified FDA of the conclusion of the

³⁷ During the 1992 meeting with the Center, Dr. Grecu asserted that he "lost the book in the first part of 1989." CX 2 at 87. In his November 1994 response to the NOOH, Dr. Grecu reiterates that "this master data book was lost in 1989, shortly after the data was statistically analyzed and prepared for publication." CX 4 at 2. When questioned by FDA investigators in June and July of 1991 regarding his missing book, the investigators noted: "he [Dr. Grecu] stated that the log was lost somewhere in the hospital about one year ago." CX 5 at 32 (emphasis added). Thus, the above statement made by Dr. Grecu during the 1991 investigation suggests that the book was lost in 1990.

Although Dr. Grecu's statements cited above are somewhat inconsistent, Dr. Grecu consistently asserts that the book was lost **before** he submitted the data for publication in the medical journal in March or April of 1989. CX 2 at 67, 87; CX 4 at 3. Thus, the weight of Dr. Grecu's testimony indicates that the book disappeared in early 1989-- the same year the study concluded.

study, required by the regulation, before the records could be destroyed. Instead, the Center alleges in its Reply Memorandum that Dr. Grecu "never informed CDER of his intent to dispose of the records of this investigation." Center Reply at 9. Dr. Grecu has, notably, never contended that he notified the Center of the conclusion of the investigation or of his intent to dispose of the records. Whether Dr. Grecu failed to notify FDA that the study had been concluded remains an unresolved issue of fact. Accordingly, I must address whether regardless of notification, Dr. Grecu nevertheless violated the regulation.

Even assuming that Dr. Grecu notified FDA that the MPA study had been discontinued, Dr. Grecu has consistently admitted that he failed to retain the records for two years after the MPA study had been discontinued. Dr. Grecu's assertion that the VA retained a similar or duplicate copy of these records for the required time period is insufficient to remove his obligation as a clinical investigator to retain his own copy of the records. I cannot determine at this point whether Dr. Grecu notified FDA that the MPA study had been discontinued. However, I do not need to reach a decision on this aspect of the charge because at a minimum, Dr. Grecu was required to retain the records for two years following completion of the study and notification of FDA, and Dr. Grecu has admitted that he personally failed to retain the medical records for the MPA study for two years after the MPA study had been discontinued. Therefore, I find that the Center has demonstrated that Dr. Grecu failed to raise any genuine and substantial issue of fact as to whether he retained the records of the MPA study for two years following completion of the study and notification to the agency, in violation of 21 C.F.R. § 312.62(c).

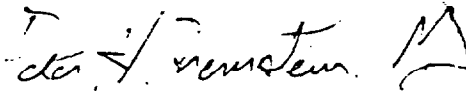
Finally, regarding all of the charges, Dr. Grecu has alleged that a physician at the Sacramento VA has had a "vendetta" against him because Dr. Grecu attempted to remove from the VA a personal friend of the physician's for substandard performance. Grecu Motion at 33-34. While I have taken note of Dr. Grecu's allegations regarding the vendetta which, according to him, prompted the initial inspections of Dr. Grecu's studies, I am still bound by the uncontested facts above to reach the conclusions that I have stated in this summary decision.

CONCLUSION

After reviewing the charges and the evidence presented by both parties, I find that Dr. Grecu deliberately or repeatedly failed to maintain adequate and accurate case histories for both the glipizide study and the MPA study in violation of 21 C.F.R. § 312.62(b). I further find that Dr. Grecu deliberately or repeatedly submitted false information to a sponsor in required reports, in violation of 21 C.F.R. § 312.70(a). Finally, I find that Dr. Grecu failed to retain the records of the MPA study for two years after the investigation had been discontinued in violation of 21 C.F.R. § 312.62(c). Dr. Grecu has raised no genuine and substantial issue of fact with regard to these three charges. Based on the evidence thus far presented, I am unable to resolve on summary decision the third charge, involving the alleged failure to obtain informed consent in violation of 21 C.F.R. § 312.60.

7. RECOMMENDATION

Based on my findings as set forth above, I recommend that the Commissioner disqualify Eugen O. Grecu, M.D., Ph.D. from being eligible to receive investigational new drugs.

A handwritten signature in cursive script, appearing to read "Peter Rheinstein", followed by a large, stylized initial "R".

Peter Rheinstein, M.D., J.D.

AUG 19 1998

Presiding Officer